EXHIBIT F

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ORIGINAL ARTICLE

Occupational and non-occupational attributable risk of asbestos exposure for malignant pleural mesothelioma

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ABSTRACT

Objectives To estimate the proportion of pleural mesothelioma cases that can be attributed to asbestos exposure in France including non-occupational exposure.

Methods A population-based case-control study including 437 incident cases and 874 controls was conducted from 1998 to 2002. Occupational and non-occupational asbestos exposure was assessed retrospectively by two expert hygienists. ORs of pleural mesothelioma for asbestos-exposed subjects compared to non-exposed subjects, and population-attributable risk (ARp) of asbestos exposure were estimated using a conditional logistic regression.

Results A clear dose-response relationship was observed between occupational asbestos exposure and pleural mesothelioma (OR=4.0 (99% CI 1.9 to 8.3) for men exposed at less than 0.1 f/mL-year vs 67.0 (99% CI 25.6 to 175.1) for men exposed at more than 10 f/mL-year). The occupational asbestos ARp was 83.1% (99% CI 74.5% to 91.7%) for men and 41.7% (99% CI 25.3% to 58.0%) for women. A higher risk of pleural mesothelioma was observed in subjects non-occupationally exposed to asbestos compared to those never exposed. The non-occupational asbestos ARp for these subjects was 20.0% (99% CI −33.5% to 73.5%) in men and 38.7% (99% CI 8.4% to 69.0%) in women. When considering all kinds of asbestos exposure, ARp was 87.3% (99% CI 78.9% to 95.7%) for men and 64.8% (99% CI 45.4% to 84.3%) for women.

Conclusions Our study suggests that the overall ARp in women is largely driven by non-occupational asbestos exposure arguing for the strong impact of such exposure in pleural mesothelioma occurrence. Considering the difficulty in assessing domestic or environmental asbestos exposure, this could explain the observed difference in ARp between men and women.

Key messages

What is the key question?

- What is the overall impact of asbestos exposure including non-occupational exposure on pleural mesothelioma?

What is the bottom line?

- Occupational asbestos exposure explains less than half the pleural mesothelioma cases among women, thus, there is a need to quantify the impact of non-occupational asbestos exposure for pleural mesothelioma.

Why read on?

- This study provides insights regarding non-occupational exposure impact in pleural mesothelioma occurrence, especially among women.

INTRODUCTION

Malignant mesothelioma is a rare tumour mostly located in the pleura and associated with poor survival. To date, asbestos and erionite fibres are the only recognised risk factors for pleural mesothelioma.[1 2]

Asbestos had been extensively used in many industries all around the world, and was progressively banned in most industrialised countries, with such action taking place first in Europe in the 1980s and specifically in 1997 in France. However, asbestos is still produced and used in many countries, most of them being developing countries. This massive use of asbestos fibres has been correlated with an increase in the incidence of asbestos-related diseases and, in particular, pleural mesothelioma.[3]

The causal relationship between occupational asbestos exposure and pleural mesothelioma is already well established,[4–13] and it is estimated that approximatively 80% of male cases may be attributed to occupational asbestos exposure. Although the role of non-occupational asbestos exposure (para-occupational, domestic or environmental) in the occurrence of pleural mesothelioma has already been demonstrated,[14–16] there is a need to quantify the risk attributable to such exposure, especially in women in whom only 40% of cases can be explained by occupational exposure.[10] Knowledge about overall asbestos exposure (occupational and/or non-occupational exposure) attributable risk could provide further information regarding the aetiology of pleural mesothelioma and could be useful to help authorities for prevention in situations where asbestos-containing materials still persist in developed countries, and where asbestos is still in use in developing countries.

In France, the National Mesothelioma Surveillance Program (PNSM) was set up in 1998

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to provide relevant information on the health effects of asbestos exposure on the French population. It relies on the exhaustive recording of all incident primary pleural tumours in specified districts.[17]

The present study reports the occupational, non-occupational and overall asbestos exposure-attributable risk for pleural mesothelioma from a population-based case-control study carried out between 1998 and 2002.

MATERIALS AND METHODS

Study design

The study design was previously reported in detail.[18] Cases were identified through the PNSM from 1998 to 2002 and certified by a standardised diagnostic confirmation procedure.[17] Two controls, selected from the general population, were matched with cases for sex, age (±5 years) and district of residence. Participation rates of cases and controls were 61.1% and 20.8%, respectively.

Trained interviewers administered a standardised questionnaire to each subject. Only subjects alive at the time of the interview were included. Information about lifetime residential, educational and occupational history (including details on job tasks and do-it-yourself activities), demographic characteristics including the socioeconomic category defined by the last occupation held, previous respiratory diseases, occupations of partners and parents, and family cancer history were collected. A more specific part of the questionnaire focused on specific lifetime situations that might have involved asbestos exposure, for example, spraying fibres, asbestos cement disposal and removal, other insulation with asbestos-containing products (sheets, ropes, gaskets, etc), brake and clutch repairs, and washing asbestos-contaminated clothes. Additional questions concerned other suspected risk factors such as ionising radiations, and man-made mineral fibres (glass fibres and mineral wool, refractory ceramic fibres). Each job held for more than 6 months was coded according to international and national classifications for occupations and industries.

The PNSM obtained the appropriate institutional review board authorisations. Written informed consent for participation in the study was obtained from all participants.

Asbestos exposure assessment

Asbestos exposure was assessed by retrospective expertise.[8 18] Two experts (an industrial hygienist and an occupational physician) analysed each subject's questionnaire blinded to case-control status.[19]

For occupational exposure, each job held for at least 6 months by a subject was translated into four semiquantitative occupational asbestos exposure parameters, including the probability of exposure (possible, definite), frequency of exposure (sporadic, intermittent, frequent or continuous), intensity of exposure (low, medium, high, very high), and the route of exposure (direct, indirect). Table 1 describes these exposure parameters. A subject occupationally exposed to asbestos was defined as a subject who had held at least one job with a non-null probability of exposure. For each subject, the maximal probability of exposure, duration of exposure (years), age at first exposure (years), time since first exposure (years), year at first exposure and a cumulative exposure index (CEI, expressed in fiber/mL-years) were defined. The CEI was calculated by summing the products of probability, frequency, intensity and duration of exposure of each job held by a given subject. Since job occupational exposure parameters are semiquantitative, numerical values were assigned to each of them (table 1). These assigned values were the same as those defined in a previous mesothelioma French case-control study,[8] where authors concluded that these values had the best ability to show a clear dose-response relationship.

Table 1 Description of the exposure parameters used to assess asbestos exposure at job level

Asbestos exposure parameters	Definition	Numerical values*
Probability of exposure	Degree of confidence that exposure really occurred, expressed in percent (%)	
Not exposed	0	0
Possible	>0–50	0.5
Definite	>50–100	1
Frequency of exposure	*Expressed in percent of work time (%)*	
Sporadic	>0–5	0.025
Occasional	>5–30	0.25
Frequent or continuous	>30–100	0.75
Intensity of exposure	Expressed in f/mL	
Low	>0–0.1	0.1
Medium	>0.1–1	1
High	>1–10	10
Very high	>10	100

*Numerical values assigned to each category in order to calculate cumulative exposure index.

Lifetime non-occupational asbestos exposure was also assessed by expertise using information reported by subjects on the use of asbestos-containing materials or performed tasks. The probability, frequency and intensity of exposure, and the route of exposure (domestic, para-occupational and environmental) were assigned to each subject. The definitions of probability, frequency and intensity of exposure were the same as for occupational exposure, except for intensity where the 'low' category was split into 'very low' and 'low'. Domestic exposure was defined by do-it-yourself activities that might have involved asbestos-containing products, for example, home improvements, and brake and clutch repairs. Para-occupational exposure was considered with regard to asbestos-contaminated clothes of relatives, partners and parents who had jobs well known to be associated with asbestos exposure, or with a high risk for pleural mesothelioma. For environmental exposure, only self-reported living near an industrial source of asbestos was considered.[18]

Statistical analysis

Analyses were performed separately for men and women. ORs and 99% CIs were estimated for the occupational and non-occupational asbestos exposure parameters using conditional logistic regression models for matched sets. All continuous exposure variables were arbitrarily categorised: duration of exposure; 1–10/>10–20/>20 years; age at first exposure: ≤15/>15–20/>20 years; time since first exposure: >19–40/>40–50/>50 years; year at first exposure: >1960/>1960–1977/>1977; CEI: >0–0.1/>0.1–1/>1–10/>10 'f/mL-years'(table 4). All population-attributable risks (ARp) and 99% CIs were calculated using the Mantel–Haenszel estimation.[20] The non-occupational asbestos exposure ARp was estimated among matched sets where cases and controls were not occupationally exposed to asbestos. Considering all asbestos exposure, the overall ARp was estimated using OR comparing

subjects occupationally and/or non-occupationally exposed to those never exposed at all. Given the long latency period of pleural mesothelioma, exposures occurring less than 20 years before diagnosis were not taken into account.[8] Although asbestos exposure was retrospectively assessed by two experts in the domain, this expertise was mainly based on subjects' self-reported tasks or asbestos-containing materials used. Thus, we conducted several sensitivity analyses by setting as not exposed: (1) subjects initially assessed as possibly exposed; (2) subjects initially assessed as exposed at a very low intensity; (3) subjects initially assessed as possibly exposed at a very low intensity; (4) subjects initially assessed as possibly exposed or exposed at a very low level intensity. We also performed additional analyses by setting the lag period at 0, 10 and 30 years.

RESULTS

The study sample comprised 437 cases (362 men, 75 women) and 874 controls (724 men, 150 women). Table 2 presents the main subjects' characteristics. Cases were ascertained in average near 12 months after they had been identified, but they were interviewed before the certification of the diagnosis and, on average, 3 months after they had been recorded. The socio-economic category differed between cases and controls: 59.4% of male cases were blue-collar workers versus 32.2% for controls. Among females, 41.1% of cases were clerical and related, workers versus 28.5% of controls.

Table 3 presents the 10 most frequent occupations and industries among males. There was a slight variation in the proportion of occupations held by male cases and controls. For some occupations, the occurrence of asbestos exposure within those occupations differed between cases and controls; that is, 90.7% of cases who ever held an occupation as sheet-metal workers were exposed to asbestos within this occupation versus 77.8% of controls.

The relationship between pleural mesothelioma and occupational asbestos exposure is reported in table 4. Among men, ORs for pleural mesothelioma were significantly increased for all exposure parameters, and a dose-response relationship was observed for all of them. OR for men exposed at less than 0.1 f/mL-years compared to those never exposed was 4.0 (99% CI 1.9 to 8.3) vs 67.0 (99% CI 25.6 to 175.1) in men exposed at more than 10 f/mL-years. Among women, a significant association between occupational asbestos exposure and pleural mesothelioma was also observed, OR for women ever exposed compared to those never exposed was 12.0 (99% CI 3.5 to 41.7). The estimated occupational asbestos exposure ARp was 83.1% (99% CI 74.5% to 91.7%) in men and 41.7% (95% CI 25.3% to 58.0%) in women.

Table 5 presents the association between non-occupational asbestos exposure and pleural mesothelioma among subjects never occupationally exposed, that is, 9 matched sets among males (9 cases and 18 controls) and 36 matched sets among females (36 cases and 72 controls). OR for men ever non-occupationally exposed to asbestos compared to those never exposed was 2.4 (99% CI 0.2 to 26.7) and increased to 4.3 (99% CI 1.2 to 15.1) for women. The non-occupational asbestos ARp for subjects never occupationally exposed was 20.0% (99% CI −33.5% to 73.5%) in men and 38.7% (99% CI 8.4% to 69.0%) in women.

The ARp related to overall asbestos exposure (occupational and non-occupational) is presented in table 6. The risk of pleural mesothelioma was strongly associated with asbestos exposure with a slight difference between men (OR=13.0 (99% CI 6.2 to 27.5)) and women (OR=8.0 (99% CI 2.9 to 21.8)).

Table 2 Main characteristics of subjects: 437 cases (362 men; 75 women) and 874 controls (724 men; 150 women), French case-control study, 1998–2002

	Men (1 086)				Women (225)			
	Cases (362)		Controls (724)		Cases (75)		Controls (150)	
	n	%	n	%	n	%	n	%
Age (years)								
Mean (SD)	67.6 (9.3)		66.8 (9.1)		66.6 (9.1)		65.8 (8.9)	
Range	41–93		41–89		41–92		41–89	
Education level (years)								
≤14	185	51.1	275	38.0	33	44.0	60	40.0
>14	177	48.9	449	62.0	42	56.0	90	60.0
Diagnostic-ascertainment period (months)								
Mean (SD)	12.7 (18.8)				12.1 (15.2)			
Range	0–97.1				0.2–65.9			
Diagnostic-interview period (months)								
Mean (SD)	3.4 (3.9)				3.4 (4.4)			
Range	0–43.7				0–36.3			
Last held occupation (ISCO 1968 major group)*								
0/1 Professional, technical and related workers	49	13.5	146	20.2	5	6.9	31	21.5
2 Administrative and managerial workers	15	4.1	68	9.4	3	4.1	1	0.7
3 Clerical and related workers	34	9.4	91	12.6	30	41.1	41	28.5
4 Sales workers	23	6.4	69	9.5	7	9.6	13	9.0
5 Service workers	16	4.4	48	6.6	16	21.9	34	23.6
6 Agricultural, animal husbandry and forestry workers; fishermen; hunters	10	2.8	69	9.5	3	4.1	4	2.8
7/8/9 Production and related workers, transport equipment operators and labourers	215	59.4	233	32.2	9	12.3	20	13.9

*Among women, two cases and six controls had never worked.

Table 3 Occupational asbestos exposure: proportion of exposed men in the most represented occupations and industries, French case-control study, 1998–2002

	Cases (362)				Controls (724)			
	n	%	Exposed within job		n	%	Exposed within job	
			n	%			n	%
Occupations (ISCO Edition 1968)								
8-73 Sheet-metal workers	54	14.9	49	90.7	27	3.7	21	77.8
8-49 Machinery fitters, machine assemblers n.e.c.*	46	12.7	31	67.4	37	5.1	25	67.6
7-00 Production supervisors and general foremen	44	12.2	31	70.5	56	7.7	40	71.4
8-71 Plumbers and pipe fitters	39	10.8	36	92.3	14	1.9	12	85.7
8-41 Machinery fitters and machine assemblers	37	10.2	21	56.8	30	4.1	13	43.3
9-99 Labourers n.e.c.*	36	9.9	24	66.7	27	3.7	15	55.6
6-21 General farm workers	31	8.6	0	0.0	86	11.9	4	4.7
9-51 Bricklayers, stonemasons and tile setters	29	8.0	25	86.2	31	4.3	26	83.9
8-34 Machine-tool operators	26	7.2	14	53.8	29	4.0	7	24.1
9-54 Carpenters, joiners and parquetry workers	26	7.2	21	80.8	27	3.7	20	74.1
Industries (ISIC Revision 2)								
5000 Construction	129	35.6	109	84.5	140	19.3	105	75.0
3841 Ship building and repairing	65	18.0	58	89.2	20	2.8	19	95.0
3813 Manufacture of structural metal products	52	14.4	43	82.7	30	4.1	20	66.7
1110 Agriculture and livestock production	48	13.3	5	10.4	145	20.0	32	22.1
6200 Retail trade	33	9.1	8	24.2	94	13.0	19	20.2
6100 Wholesale trade	29	8.0	9	31.0	74	10.2	13	17.6
3819 Manufacture of fabricated metal products except machinery and equipment n.e.c.*	24	6.6	13	54.2	24	3.3	6	25.0
9100 Public administration	24	6.6	6	25.0	71	9.8	11	15.5
3845 Manufacture of aircraft	23	6.4	10	43.5	27	3.7	10	37.0
9310 Education services	23	6.4	9	39.1	82	11.3	19	23.2

*n.e.c.: not elsewhere classified.

The overall asbestos exposure ARp was 87.3% (99% CI 78.9% to 95.7%) in men and 64.8% (99% CI 45.4% to 84.3%) in women.

From the sensitivity analysis, in men, the overall ARp was 68.6% (99% CI 58.0 to 79.1), 85.9% (99% CI 77.2 to 94.7), 86.0% (99% CI 77.2 to 94.7) and 68.6% (99% CI 58.0 to 79.1) for analyses 1, 2, 3 and 4, respectively. In women, the overall ARp was 26.7% (99% CI 12.0 to 41.3), 47.4% (99% CI 30.0 to 65.0), 52.0% (99% CI 34.1 to 69.8) and 22.0% (99% CI 8.0 to 36.0) for analyses 1, 2, 3 and 4, respectively (see online supplementary material).

DISCUSSION

This study permits to quantify the role of some aspects of non-occupational asbestos exposure in the occurrence of pleural mesothelioma. When taking into account all kinds of asbestos exposure, 87.3% of male cases and 64.8% of female cases were attributable to asbestos.

In table 3, we observed an intravariability of asbestos exposure within each occupation and industry category. This is due to the exposure assessment method that incorporated experts' knowledge about that occupation or industry, as well as specific tasks performed, and circumstances of asbestos exposure reported by the subject himself.

The relationship between occupational asbestos exposure and occurrence of pleural mesothelioma is now well known. To date, several case-control studies have analysed this relationship, and all confirmed the causal link between occupational asbestos exposure and pleural mesothelioma,[4 5 7–13 21] but few have estimated the population-attributable risk of asbestos exposure for pleural mesothelioma.[4 5 10 13] Results from the present study are consistent with the literature. However, they may not be generalisable to countries, such as developing countries, countries with different pattern of industrialisation, or which used different type of asbestos fibres.

In France, almost all the asbestos used was imported, and chrysotile seems to have been the most common used type. Sources of asbestos exposure came from mainly construction industry, shipbuilding and repairing industry, manufacture of asbestos cement products, metal-working industry and motor vehicles manufacture or repairing.[8]

Our results support the role of non-occupational asbestos exposure in the aetiology of pleural mesothelioma and make it possible to quantify the weight of such exposure in the occurrence of pleural mesothelioma, especially among women. There is now stronger evidence that pleural mesothelioma may be induced by non-occupational exposure. Several population-based case-control studies have established an association between para-occupational exposure and the occurrence of pleural mesothelioma,[22–24] as well as for household exposure.[7 25] A meta-analysis of eight studies provided a summary relative risk of 8.1 (95% CI 5.3 to 12.0).[26] While there is evidence of an association between asbestos exposure from a geological source and the increased incidence of pleural mesothelioma,[27] recent studies have shown an increased risk of pleural mesothelioma associated with environmental exposure related to proximity with an asbestos plant,[28 29] as well as environmental exposure due to residence near asbestos mines.[11 30] Bourdes *et al* reported a summary relative risk for environmental exposure due either to asbestos mines or an asbestos

Table 4 Occupational asbestos exposure and risk of pleural mesothelioma, 437 cases (362 men; 75 women) and 874 controls (724 men; 150 women), French case-control study, 1998–2002

		Men (1 086)							Women (225)					
		Cases (362)		Controls (724)					Cases (75)		Controls (150)			
Occupational asbestos exposure		n	%	n	%	OR	99% CI		n	%	n	%	OR	99% CI
Not exposed		28	7.7	327	45.2	1.0	–		41	54.7	139	92.7	1.0	–
Exposed		334	92.3	397	54.8	11.4	6.1 to 21.4		34	45.3	11	7.3	12.0	3.5 to 41.7
Highest probability of exposure	Possible	43	11.9	102	14.1	5.6	2.6 to 12.1	Possible	19	25.3	8	5.3	9.6	2.4 to 38.1
	Definite	291	80.4	295	40.7	13.2	7.0 to 25.0	Definite	15	20.0	3	2.0	18.2	2.9 to 112.9
Duration of exposure (years)	1–10	71	19.6	119	16.4	7.9	3.8 to 16.1	1–10	19	25.3	4	2.7	36.2	2.6 to 513.3
	>10–20	78	21.6	95	13.1	11.2	5.4 to 23.3	>10	15	20.0	7	4.6	6.6	1.6 to 27.8
	>20	185	51.1	183	25.3	13.9	7.2 to 27.0							
Age at first exposure (years)	≤15	77	21.3	63	8.7	15.8	7.4 to 33.8	≤20	14	18.7	2	1.3	38.2	2.4 to 601.3
	>15–20	122	33.7	115	15.9	14.6	7.3 to 29.4	>20	20	26.6	9	6.0	8.3	2.2 to 31.5
	>20	135	37.3	219	30.2	8.5	4.4 to 16.4							
Time since first exposure (years)	>19–40	81	22.4	119	16.4	8.3	4.0 to 17.2	>19–40	15	20.0	5	3.3	10.2	2.0 to 50.5
	>40–50	114	31.5	131	18.1	12.6	6.2 to 25.6	>40	19	25.3	6	4.0	14.2	2.7 to 75.0
	>50	139	38.4	147	20.3	13.4	6.7 to 26.8							
Year at first exposure	≤1960	256	70.7	275	38.0	13.8	7.2 to 26.7	≤1960	19	25.3	6	4.0	14.3	2.7 to 75.8
	>1960–1977	75	20.7	108	14.9	8.4	4.0 to 17.6	>1960–1977	13	17.3	4	2.7	10.6	2.1 to 55.9
	>1977	3	0.9	14	1.9	1.9	0.3 to 11.8	>1977	2	2.7	1	0.6	7.9	0.2 to 258.8
Cumulative exposure (« f/mL-years »)	>0–0.1	54	14.9	181	25.0	4.0	1.9 to 8.3	>0 to 0.1	13	17.3	6	4.0	6.9	1.5 to 30.9
	>0.1–1	68	18.8	121	16.7	8.3	3.8 to 17.7	>0.1	21	28.0	5	3.3	23.7	3.3 to 168.53
	>1–10	115	31.8	68	9.4	22.5	10.4 to 48.7							
	>10	97	26.8	27	3.7	67.0	25.6 to 175.1							
Attributable risk (99% CI) (%)						83.1 (74.5 to 91.7)							41.7 (25.3 to 58.0)	

Table 5 Non occupational asbestos exposure and risk of pleural mesothelioma among subjects non-exposed to occupational asbestos exposure, 45 cases (9 men; 36 women) and 90 controls (18 men; 72 women), French case-control study, 1998–2002

	Men						Women					
	Cases (9)		Controls (18)				Cases (36)		Controls (72)			
Non-occupational asbestos exposure	n	%	n	%	OR	99% CI	n	%	n	%	OR	99% CI
Not exposed	6	66.7	15	83.3	1.0	–	17	47.2	56	77.8	1.0	–
Exposed	3	33.3	3	16.7	2.4	0.2 to 26.7	19	52.8	16	22.2	4.3	1.2 to 15.1
Highest probability of exposure												
Possible	0	0.0	1	5.6	–	–	11	30.6	13	18.1	3.2	0.8 to 13.2
Definite	3	33.3	2	11.1	4.6	0.2 to 96.9	8	22.2	3	4.1	7.5	1.2 to 48.0
Attributable risk (99% CI) (%)					20.0 (–33.5 to 73.5)						38.7 (8.4 to 69.0)	

processing plant of 7.0 (95%CI 4.7 to 11.0). To date, there is only weak evidence of a possible effect of passive exposure in buildings containing asbestos on the occurrence of pleural mesothelioma.[15]

As in most case-control studies, the major limitation of this study is the retrospective assessment of exposure. While we are confident about the reliability of the occupational and para-occupational asbestos exposure assessment, this is not the case for domestic and environmental asbestos exposure. In the questionnaire, there were specific questions about domestic use of asbestos, or the proximity to an asbestos-processing plant. The reliability of such assessment is poor and is highly subject to recall bias.[31] Besides the proximity to an asbestos-processing plant, we did not consider other potential sources of environmental exposure, such as residence in buildings containing asbestos, or proximity to construction sites involving asbestos. Moreover, since we did not assess environmental exposure through lifetime residential distance from an asbestos-processing plant or other industrial sources but through self-report, we may have underestimated this kind of exposure, thereby leading to an underestimation of non-occupational and overall ARp. This hypothesis could explain the observed difference in ARp between men and women. Indeed, since 92% of male cases and only 45% of female cases were occupationally exposed, the ARp among women should be more affected by the bias induced by the underestimation of environmental exposure than that among men. A recent French study on the spatial distributions of male and female incidence of mesothelioma cases with and without any identified occupational or non-occupational asbestos exposure suggested the major influence of asbestos in female mesothelioma, likely through unknown environmental exposure.[32] However, we cannot exclude a possible overestimation of the non-occupational ARp and, thus, the overall ARp due to recall bias if we hypothesise that controls tended to under-report environmental or domestic exposure compared to cases. This effect might have been more extreme among women, since most cases were not occupationally exposed leading to a possible over-reporting of environmental or domestic exposure. This plausible hypothesis may also explain the observed difference between men and women for the non-occupational ARp. Indeed, from the sensitivity analyses conducted which aimed to assess the extent of this recall bias, the overall ARp varied from 68.6% to 87.3% among men, and from 22.0% to 64.8% among women. Only 11.6% of male cases were assessed as possibly exposed and 0.6% at a very low intensity versus 42.7% and 28.6% of female cases, respectively. Female cases were mainly considered as exposed at a very low intensity through domestic exposure, that is, use of baking trays, cooking gloves, toasters and ironing boards. Results from these sensitivity analyses demonstrate the difficulty of estimating precisely the overall asbestos ARp among women. Indeed, since the ARp among men is mostly driven by occupational exposure, and because the assessment of such exposure relies on the knowledge of experts in industrial hygiene, there is little impact

Table 6 All asbestos exposure and risk of pleural mesothelioma, 437 cases (362 men; 75 women) and 874 controls (724 men; 150 women), French case-control study, 1998–2002

	Men (1 086)						Women (225)					
	Cases (362)		Controls (724)				Cases (75)		Controls (150)			
All asbestos exposure	n	%	n	%	OR	99% CI	n	%	n	%	OR	99% CI
Not exposed	17	4.7	263	36.3	1.0	–	19	25.3	104	69.3	1.0	–
Exposed	345	95.3	461	63.7	13.0	6.2 to 27.5	56	74.7	46	30.7	8.0	2.9 to 21.8
Occupational only	264	76.5	317	68.7			26	46.4	9	19.6		
Non occupational only	11	3.2	64	13.9			22	39.3	35	76.1		
Occupational and non-occupational	70	20.3	80	17.4			8	14.3	2	4.3		
Highest probability of exposure												
Possible	42	11.6	104	14.4	6.8	2.8 to 16.2	32	42.7	38	25.3	5.8	2.0 to 17.0
Probable	303	83.7	357	49.3	14.8	7.0 to 31.6	24	32.0	8	5.4	14.7	4.0 to 54.2
Attributable risk (99% CI) (%)					87.3 (78.9 to 95.7)						64.8 (45.4 to 84.3)	

of the sensitivity of the 'ever exposed' definition on the ARp estimation. However, since only 40% of female cases are attributable to occupational asbestos exposure, the overall ARp in women is driven by occupational and non-occupational asbestos exposure. Thus, among women, the 'ever exposed' definition, and especially, the 'non-occupationally ever exposed' definition, has an important impact on the estimation of ARp.

The PNSM relies on the exhaustive recording of all incident primary pleural tumours in representative districts of France.[17] Only incident cases who were alive at the time of the interview were included in these analyses. From a substudy on non-response bias, it appeared that the sociodemographic characteristics of cases who died before interview or refused to answer questions, did not differ from those of the cases included in this study.[18] Cases who had died before the interview seemed to be less occupationally exposed than those included (among males, 80.3% vs 92.3%, respectively; among women, 18.7% vs 45.3%, respectively). However, occupational asbestos exposure was derived from simplified questionnaires and mainly assessed through job titles. According to controls selection, it appeared that there were more blue-collar workers among refusing controls and more white-collar workers among participating controls, leading to a possible underestimation of occupational asbestos exposure among our control population.[33]

As in all previous published population-based mesothelioma case-control studies, the prevalence of blue collar workers was higher among cases than among controls. We did not adjust for this difference in socioeconomic status between cases and controls, since this is a variable that is linked to asbestos exposure but cannot be considered as potential causal factor of pleural mesothelioma.[34]

The definition of a lag period of 20 years had no impact on results since they were similar when we implemented a lag period strategy of 0, 10 and 30 years (see online supplementary material).

Since we have performed several comparisons, we have decided to present results with 99% CIs instead of the traditional 95% CIs. In order to estimate the 99% CIs for ARp, we used a method proposed by Greenland,[20] which is based on the Mantel–Haenszel estimation and is consistent for sparse data as found in individually matched studies. Since it exists several variance formulas in the literature, we also derived 99% CIs using the bootstrap method,[35] and results were very similar (see online supplementary material).

CONCLUSION

After quantification of the role of non-occupational asbestos exposure in the occurrence of pleural mesothelioma, approximately 35% of female cases were still not attributable to asbestos exposure. Since domestic and environmental exposures are hardly identifiable, the overall ARp could be underestimated owing to the underestimation of non-occupational asbestos exposure. Explanations, such as other factors involved in the aetiology of pleural mesothelioma, are also possible.

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Notes